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CLINICOHEMATOLOGICAL PROFILES OF HEPATITIS A VIRUS (HAV): A RETROSPECTIVE STUDY

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ABSTRACT: Aim: Acute viral hepatitis A (HAV) is a major problem in parts of the developing countries. HAV is transmitted enterically and its incidence is high in places where poor hygienic conditions prevail. Most studies in the past have been on liver the primary organ affected by HAV and reports on extrahepatic organs are lacking. The present study was carried out to ascertain the alterations on the haematological, hepatic and renal parameters. **Material and Methods**: This was a retrospective study and was conducted in a tertiary care hospital in India. Data was analysed in people who expressed known symptoms of HAV and established by Anti-HAV IgM antibody. A total of 22 paediatric and 109 adult people were included in the study and compared with healthy individuals who were tested negative for infectious and chronic diseases. **Results**: The results indicated that jaundice, vomiting and fever were the predominant clinical symptom seen in both children and adults. There was significant difference in the various haematological, hepatic and electrolyte endpoints ($p < 0.05$ to 0.0001), while there was no such difference in the renal function test parameters. **Conclusion**: The present study indicates that acute infection with HAV causes alterations in haematological, hepatic parameters and in the levels of electrolytes in the serum.

KEY WORDS: Hepatitis A Virus (HAV); clinical, haematological; hepatic; renal.

INTRODUCTION:

Hepatitis A virus (HAV), a small non enveloped single-stranded RNA virus belonging to the family of Picornaviridae is an important pathogen affecting the humans [1, 2]. At a global level, HAV is the most common form of acute viral hepatitis and differences in its endemicity are closely linked to hygienic and sanitary conditions [1-3]. According to recent estimates, at a global level, 1.4 million cases of HAV infection are being reported principally in the developing countries [1, 2]. The virus is transmitted by faecal-oral route and some of the principal sources include exposure to contaminated water or consumption or handling of contaminated shellfish, fruits and uncooked vegetables [2,4]. After ingestion, the virus passes through intestinal tract and gets lodged in liver where it may replicate, interferes with liver function and triggers an immune response that

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causes liver inflammation [5]. Additionally, HAV synthesized in liver is constantly secreted in bile and is excreted (in high concentration to as high as 10^9 infectious virions per gram in) stool samples [5]. The highest faecal excretion occurs before the onset of jaundice and appearance of clinical symptoms or elevation of liver enzymes and declines after jaundice appears [5].

From a clinical perspective, HAV is a self-limiting human pathogen and can produce effects that range from a lack of symptoms to death from fulminant hepatitis [2, 6]. The incubation period for HAV infection ranges from 15-50 days and approximately 40-70% of patients develop jaundice, the main symptom, during the course of the disease [7]. The other important clinical features include fever, nausea, dark coloured urine, vomiting, malaise, abdominal tenderness, hepato-splenomegaly, lasting for few weeks [8]. With respect to the clinical infection post infection in children below the age of 6 reports suggest that more than 50% are generally asymptomatic, while the remaining 50% present with mild symptoms of which with 10% having prolonged or relapsing symptoms for nearly a year. The other most important observation is that HAV infection normally does not occur in young children and that the overall case-fatality ratio (CFR) is 0.3%[5]. On the contrary, in older children and adults, HAV infection is usually symptomatic and jaundice occurs in 70% of patients [5]. Additionally, in adults over 50 years, the CFR reported to be about 2.7% and is high in individuals with chronic liver disease, including chronic viral hepatitis [especially chronic hepatitis C] [5,9].

Laboratory abnormalities include elevations of serum transaminases (>1000 IU/dL), serum bilirubin (≤10mg/dL), and alkaline phosphatase (up to 400U/L) [10]. The elevation in bilirubin levels is usually preceded by elevation in transaminases. The increase in Serum alanine aminotransferase (ALT) is usually higher than that of the serum aspartate aminotransferase (AST). Serum aminotransferases peak around one month after exposure to the virus and then gradually decline [8]. A decline in the serum bilirubin level is observed within two weeks of peak levels [9].

From a diagnostic perspective, acute HAV infection is differentiated from other viral hepatitis by use of the highly specific anti HAV IgM-ELISA test [11]. The antibodies produced in the body reaches detectable levels in 5-10 days before the onset of symptoms and decreases within 5-6 months after recovery phase of the disease [11]. However, during convalescence, IgM is reduced and the IgG class of antibody remains predominant however, anti-HAV of the IgG class becomes the predominant antibody[12]. HAV infection does not evolve into a chronic form, and individuals who recover from infection are not reinfected. In the present study we have attempted to understand the clinical, hematological, hepato-renal parameters in people diagnosed with HAV in a tertiary care centre in a coastal Karnataka, India.

MATERIALS AND METHODS:

This was a retrospective study, conducted by Departments of Clinical Microbiology and General Medicine at Father Muller Medical College Hospital, Mangalore during January 2014 to December 2015. The study was undertaken after approval by the Institutional Ethics Committee. All patients who were admitted as in patients with acute HAV infection were included in the study. Anti HAV IgM test was performed using Enzyme "Capture" Immunoassay for IgM antibodies against HAV (ImmunoVision, USA) with sensitivity and Specificity shown as 99% as per manufacturer's instructions. All the clinical manifestations, haematological, hepatorenal parameters and treatment were considered were noted in detail for the study. For HAV negative data used as concomitant controls, people who had come for general health checkups and for skin ailments were considered. Care was taken to see that people with malaria, dengue, leptospirosis, filaria, tuberculosis, or any other infections were excluded from the study. The data from individual

patients were noted and entered in to the Microsoft excel. All the data was recorded as mean ± standard deviation (SD) and are represented in each of the tables. The demographic and treatment details were categorised in to frequency. To assess the HAV-induced changes in the paediatric and adult population the data was accordingly segregated and compared with HAV negative subjects using the student's "t" test. A p value of 0.05 was considered significant.

RESULTS:

Table 1: Incidence and mean number of days in various clinical symptoms observed in children and adults afflicted with hepatitis A

	CHILDREN		ADULTS	
	Percentage	Mean days	Percentage	Mean days
FEVER	71.42 (15/22)	5.06±2.98 (2-14 days)	53.38 (63/118)	5.41±2.98 (2-15 days)
PAIN ABDOMEN	38.09 (8/22)	3.5±3.52 (1-14 days)	23.72 (28/118)	3.64±2.87 (1-10 days)
VOMITING	33.33 (7/22)	3.36±2.2 (1-7 days)	40.67 (48/118)	3.62±2.23 (1-10 days)
NAUSEA	28.57 (6/22)	2.16±0.75 (1-3; days)	5.08 (6/118)	4.66±2.51 (2-7 days)
HEADACHE	19.04 (4/22)	2.00±0.81 (1-3; days)	5.08 (6/118)	4.25±2.06 (2-7 days)
MYALGIA	33.33 (7/22)	2.00±0.71 (1-3; days)	10.16 (12/118)	3.5±2.12 (2-5 days)
JAUNDICE	47.61 (10/22)	1.71±0.75 (1-3; days)	28.81 (34/118)	3.5±2.12 (2-5 days)
YELLOWISH DISCOLORATION OF URINE	42.85 (9/22)	3.75±2.57 (1-7; days)	9.32 (11/118)	6.33±8.84 (1-45 days)
DIARRHEA	9.52 (2/22)	2.00±0.7 (1-3; days)	3.38 (4/118)	3±2.71 (1-7 days)
ALTERED SENSORIUM	**4.76 (1/22)**	**1.5±0.71 (1-2; DAYS)**	**2.54 (3/118)**	**4.25±5.18 (1-12 DAYS)**

In the present study a total of 22 paediatric and 109 adult patients with only HAV infection were admitted during the study time period of January 2014-December 2015. The average inpatient days were observed to be 4.68±2.89 for children and 6.02±2.43 for adults. The patients presented predominately with jaundice along with fever, pain in abdomen, vomiting, nausea, headache, body ache, myalgia, yellowish urine, diarrhoea and altered sensorium (Table 1). The average admission was observed to be 4.68±2.89 for children and 6.02±2.43 for adults. The patients presented predominately with jaundice in both children and adults along with fever, pain in abdomen, vomiting, nausea, headache, body ache, myalgia, yellowish urine, diarrhoea and altered sensorium for various time periods (Table 1).

There was only one death due to HAV during the study period. A girl aged 3 years from a very remote village had presented with fever, irritability and altered sensorium for 4 days. On examination, she was found to be icteric and had acidotic breathing. Her blood investigation revealed to be anaemic (Hb-10.2 g %), with acute fulminant hepatic failure (serum albumin -2.94 g%, serum total bilirubin -7.99 mg %) and severe metabolic acidosis (arterial blood pH – 7.12). In spite of mechanical ventilatory support, fresh frozen plasma transfusion and other supportive measures, she expired within 24 h of admission due to acute fulminant hepatic failure with metabolic acidosis.

With respect to the hematological parameters in children a significant difference in the eosinophils ($p < 0.002$), monocytes ($p < 0.0008$) and ESR ($p < 0.009$) was observed; while in adults the changes were seen in levels of Hb ($p < 0.0001$), TC ($p < 0.0001$), PCV ($p < 0.046$), lymphocytes ($p < 0.027$), eosinophils ($p < 0.002$), monocytes ($p < 0.0001$) (Table 2, 3). The liver function parameters indicated that in children a significant difference was seen in protein ($p < 0.03$), bilirubin ($p < 0.0001$), AST ($p < 0.0001$), ALT ($p < 0.0003$) and ALP ($p < 0.01$); while in adults protein ($p < 0.0001$), globulin ($p < 0.0.032$), A/G ratio ($p <$

0.0.0001), bilirubin (p <0.0001), AST (p < 0.0001), ALT (p <<.0001), ALP (p < 0.018) (Table 2, 3). Alterations were also seen in levels of serum electrolytes and were significantly altered in all the three in children [Na^+ (p < 0.03), K^+ (p < 0.0001) and Cl^- (p < 0.01)], while in adults it was statistically significant only for K^+ (p < 0.0001) (Table 2, 3). However statically significant difference was not seen with the renal parameter's urea and creatinine.

Table 2: Comparison of the haematological and biochemical parameters in children affected by HAV

	CONTROL CHILDREN MEAN±SD (MIN – MAX; N)	CHILDREN AFFECTED BY HAV MEAN±SD (MIN – MAX; N)	P
AGE	12.04±4.35 (4-17; N =93)	11.59±3.77 (4-17; N =22)	
HB	12.52±1.44 (9.2-15.9; N =93)	12.83±1.81 (8.9-16.3; N =21)	0.46
TC	8448.17±5508.93 (2100-54000; N =93)	8819.04±6743.93 (3800-28100; N =21)	0.81
N	56.06±9.48 (36-89; N =93)	59.60±16.87 (29-93; N =20)	0.37
L	36.68±9.43 (9-55; N =93)	32.65±15.84 (6-68; N =20)	0.28
E	4.41±5.11 (1-26; N =93)	2.40±1.56 (1-5; N =20)	0.002
M	2.41±1.67 (0-11; N =93)	6.88±4.48 (1-13; N =17)	0.0008
ESR	9.66±5.64 (1-25; N =59)	21.47±16.46 (4-55; N =17)	0.009
PCV	42.75±5.08 (34.42-49.8; N =15)	44.78±4.42 (38.7-49.8; N =5)	0.41
S. PROTEINS.	7.22±0.60 (6.51-8.25; N =17)	6.65±0.80 (4.5-8.14; N =15)	0.03
ALBUMINS.	4.27±0.83 (3.4-7.17; N =17)	3.94±1.00 (2.94-7.17; N =15)	0.31
GLOBULIN	3.00±0.46 (2.25-3.8; N =17)	2.88±0.58 (1.6-3.8; N =15)	0.49
A/G RATIO	1.46±0.39 (1.06-2.47; N =17)	1.28±0.29 (0.9-2; N =13)	0.17
BILIRUBIN	0.62±0.40 (0.2-2.1; N =24)	3.48±2.15 (0.3-8.15; N =22)	<.0001
AST	28.36±12.10 (13-64; N =24)	1610.38±2711.45 (60-12198; N =21)	0.0001
ALT	25.12±20.29 (10-115; N =24)	1283.00±1378.11 (106-5170; N =22)	0.0003
ALP	95.66±42.75 (25-160; N = 15)	451.30±564.28 (35-2737; N =20)	0.01
NA	138.13±6.77 (128-148; N = 15)	133.60±2.59 (128-137; N =10)	0.03
K	4.38±0.53 (3.5-5.3; N = 15)	4.30±0.44 (3.35-5.18; N =10)	<.0001
CL	98.66±6.09 (85-105; N = 15)	93.08±4.04 (86.4-99.3; N =10)	0.01
UREA	20.74±8.38 (10-38; N =43)	18.33±5.63 (10-28; N =12)	0.25
CREATININE	**0.74±0.24 (0.5-1.4; N =45)**	**1.34±2.59 (0.45-10.3; N =14)**	**0.40**

Table 3: Comparison of the hematological and biochemical parameters in adults affected by HAV

ADULT	CONTROLS MEAN±SD (MIN – MAX; N)	HEPATITIS A VIRUS INFECTED MEAN±SD (MIN – MAX; N)	P
AGE	32.14±7.10 (18-45; N = 105)	33.91±8.10 (18-69; N = 109)	
HB	12.48±1.07 (9-15.4; N =105)	13.36±1.89 (8-18.5; N = 97)	0.0001
TC	8311.42±1765.28 (5100-13600; N =105)	6168.31±2588.85 (2600-14800; N = 101)	<.0001
N	60.1±9.69 (36-82; N =105)	59.88±13.08 (23-82; N = 93)	0.91
L	32.12±9.29 (14-54; N =105)	30.77±11.28 (8-70; N = 93)	0.027
E	4.32±2.53 (1-9; N =105)	3.20±2.51 (1-14; N = 89)	0.002
M	4.10±0.59 (1-4; N =105)	6.56±4.67 (1-13; N = 87)	<.0001
ESR	5.35±1.89 (2-9; N =105)	20.54±17.95 (2-104; N = 77)	<.0001
PCV	39.99±4.15 (33.9-47.8; N =105)	41.90±4.50 (31.5-51.6; N = 29)	0.046
S. PROTEIN	7.30±0.42 (6.4-8.2; N =98)	6.86±0.59 (4.54-8.03; N = 99)	<.0001
S. ALBUMIN	4.29±0.43 (3.12-5.07; N =98)	3.81±0.42 (2.17-4.89; N = 99)	<.0001
S. GLOBULIN	2.97±0.32 (2.4-3.5; N =98)	3.02±0.43 (1.4-4; N = 99)	0.25
A/G RATIO	1.46±0.25 (0.9-1.9; N =98)	1.24±0.25 (0.8-2; N = 99)	0.032
BILIRUBIN	0.66±0.40 (0.2-2.1; N =105)	4.96±5.44 (0.3-29.3; N = 109)	<.0001
AST	23.37±8.36 (10-60; N =105)	1406.54±2286.79 (15-14638; N = 105)	<.0001
ALT	22.84±12.55 (10-83; N =105)	1480.57±1652.02 (10-9449; N = 105)	<.0001
ALP	74.17±18.94 (38-108; N =98)	152.87±91.40 (41-620; N = 91)	<.0001
NA	137.79±13.57 (1.37-143.8; N =105)	134.36±3.66 (126-140; N = 46)	0.018
K	4.25±0.38 (3.6-5.07; N =105)	4.16±0.47 (3.24-5.41; N = 46)	0.22
CL	100.74±9.97 (2.3-106; N	94.95±4.30 (85.1-106; N = 41)	<.0001

	=105)		
UREA	21.41±7.84 (10-40; N =105)	22.92±33.59 (10-258; N = 55)	0.74
CREATININE	**0.79±0.20 (0.49-1.35; N =105)**	**1.65±4.96 (0.5-39; N = 60)**	**0.18**

DISCUSSION:

In this study it was observed that fever was the most commonly observed presentation in the affected children (71.42%) and adults (53.38%) (Table 1). The other most commonly observed presentations were jaundice, nausea, vomiting, pain in the abdomen and myalgia and are in agreement to earlier reports (Franco et al., 2012). The other most important observations are that other than fever, the other incidence and the percent affected with other clinical presentations was diverse in children and in adults substantiating reports that the expression of clinical symptoms varies greatly with the age of the infected person [(13)]. Only one death was observed in the study period, also validating the fact that HAV rarely is fatal [(1-3. 13)].

With respect to the haematological parameters the results indicated that in children a significant difference was seen in the eosinophilic levels (4.41±5.11 in control vs 2.40±1.56 in HAV; $p < 0.002$) and that this trend was not seen in adults. This difference is attributable to the fact that majority of the controls were children who had come with allergic issues while in the adults majority were healthy individuals who came for a routine health care checkup. The other important observation was that the levels of monocytes were high in HAV infected children (2.41±1.67 in control vs 6.88±4.48 in HAV; p 0.0008) and adults (4.10±0.59 in control vs 6.56±4.67 in HAV; $p < 0.0001$). Monocytosis is seen in the recovery phase of many acute infections and these observations indicate that the recuperation stage [(14)].

With respect to the biochemical parameters in this study we observed deranged liver function test validating the universal fact that HAV causes liver damage [2-5]. Further a decrease in serum albumin was seen only in adults indicating that they had more severe acute hepatic injury validating the previous reports [(11-15)]. The fact that needs to be considered and at all points is that the elevated levels of the liver enzymes (ALT, AST) return to normal range within 5-20 weeks[11-15], while that of total bilirubin levels which are also elevated and remain high for several weeks [14-16]. Among the dyselectremia in HAV infected children, hyponatremia was most common, and this could be because 33% children had more gastrointestinal symptoms (vomiting). The serum creatinine and blood urea levels were not altered validating the fact that in acute conditions HAV does not affect the kidney function.

CONCLUSIONS:

The results from the present study indicate that infection with HAV causes alteration in haematological, hepatic and investigates the clinical symptoms and alterations in haematological and crucial blood parameters in acute HAV infection. A literature study shows that there have been no studies addressing these aspects in totality from India. Future studies are required to observe the time taken to recover after acute HAV infection and its impact on the individual.

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